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Fully automated segmentation of the cervical cord from T1-weighted MRI using *PropSeg*: Application to multiple sclerosis☆

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ABSTRACT

Spinal cord (SC) atrophy, i.e. a reduction in the SC cross-sectional area (CSA) over time, can be measured by means of image segmentation using magnetic resonance imaging (MRI). However, segmentation methods have been limited by factors relating to reproducibility or sensitivity to change. The purpose of this study was to evaluate a fully automated SC segmentation method (*PropSeg*), and compare this to a semi-automated active surface (*AS*) method, in healthy controls (HC) and people with multiple sclerosis (MS). MRI data from 120 people were retrospectively analysed; 26 HC, 21 with clinically isolated syndrome, 26 relapsing remitting MS, 26 primary and 21 secondary progressive MS. MRI data from 40 people returning after one year were also analysed. CSA measurements were obtained within the cervical SC. Reproducibility of the measurements was assessed using the intraclass correlation coefficient (ICC). A comparison between mean CSA changes obtained with the two methods over time was performed using multivariate structural equation regression models. Associations between CSA measures and clinical scores were investigated using linear regression models. Compared to the *AS* method, the reproducibility of CSA measurements obtained with *PropSeg* was high, both in patients and in HC, with ICC > 0.98 in all cases. There was no significant difference between *PropSeg* and *AS* in terms of detecting change over time. Furthermore, *PropSeg* provided measures that correlated with physical disability, similar to the *AS* method. *PropSeg* is a time-efficient and reliable segmentation method, which requires no manual intervention, and may facilitate large multi-centre neuroprotective trials in progressive MS.

1. Introduction

Neuropathological and magnetic resonance imaging (MRI) studies have demonstrated the involvement of the spinal cord (SC) in multiple sclerosis (MS); neurodegeneration in the SC is thought to represent the main pathological substrate of irreversible locomotor disability (Abdel-Aziz et al., 2015; DeLuca et al., 2006; Ganter et al., 1999). In particular, SC MRI has provided indirect evidence of axonal degeneration by quantifying atrophy, i.e. a reduction in SC cross-sectional area (CSA) over time, with correlations identified between measures of CSA and physical disability (Kearney et al., 2015b; Lin et al., 2004; Losseff et al., 1996). Such associations support the notion that reliable CSA estimation over time could be a plausible endpoint for clinical trials for neuroprotection in MS (Kearney et al., 2014a), and a number of exploratory studies have been reported in the literature (Kalkers et al., 2002; Leary et al., 2003).

Previous methods used for measuring CSA have been variable in terms of their reproducibility and sensitivity to small change, and all of them require some degree of operator input (Coulon et al., 2002; Horsfield et al., 2010; Kawahara et al., 2013; Kidd et al., 1993; McIntosh et al., 2011). Typically, intra- and inter-observer reproducibility is assessed from repeated measurements by estimating the coefficient of variation (COV); the currently established semi-automated active surface (*AS*) method offers intra- and inter-observer COV values of 0.44% and 1.07%, respectively (Horsfield et al., 2010). More recently, investigators

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have aimed to develop fully automated segmentation methods, which may minimize user-bias and significantly reduce the image processing time (Asman et al., 2014; Chen et al., 2013; Koh et al., 2011).

However, the variety of image acquisitions, the types of image contrast and variability of the field of view (FOV) required for each specific application, make it particularly challenging for each individual method to simultaneously account for so many variables. A fully automated method, called *PropSeg*, which accounts for such variability, has been recently developed (De Leener et al., 2014). *PropSeg* is based on an iterative propagation of a deformable model with adaptive contrast mechanisms and offers fast and reliable measurements of the cord CSA in a matter of seconds, as demonstrated in a pilot study of healthy volunteers and people with spinal cord injury (De Leener et al., 2014); importantly, the method has been reported to work when using T1-, T2- and T2*-weighted acquisitions and at any level of the spinal cord.

In this study we evaluate *PropSeg*, as compared to the widely used semi-automated *AS* method (Horsfield et al., 2010), in a large cohort of healthy controls and people with MS, in order to test the following hypotheses:

(i) *PropSeg* provides reproducible CSA measurements in the cervical SC.
(ii) A reduction in CSA in the cervical SC, seen longitudinally in MS, can be reliably measured with *PropSeg*.
(iii) There are associations between cervical SC CSA measures derived by *PropSeg* and clinical scores in MS.

2. Materials and methods

2.1. Study participants

MRI data from 120 people were retrospectively analysed; 26 healthy controls (HC), 21 people with clinically isolated syndrome (CIS), 26 relapsing remitting (RR) MS, 21 secondary progressive (SP) MS and 26 primary progressive (PP) MS. The inclusion criteria for the CIS cohort, and the criteria used for MS diagnosis and MS subgroup classification, have been reported previously (Kearney et al., 2014b, 2015a).

All people with CIS and MS had Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) and Multiple Sclerosis Functional Composite (MSFC) score (Fischer et al., 1999) determined by the same neurostatus certified assessor. Z-scores for the 25-foot timed walk test (TWT), 9-hole peg test (HPT) and 3 s paced auditory serial addition test B (PASAT) were calculated using published normative values. For those participants who could not perform the TWT and HPT, an arbitrary value of 180 s or 300 s was assigned to that test, respectively. In addition, the American Spinal Injury Association (ASIA) motor (m) and sensory (s) scores (Maynard et al., 1997) were recorded for all participants. All clinical assessments were performed immediately before the MRI study. Demographic and clinical characteristics are summarised in Table 1.

A total of 40 people returned for follow-up assessment, with MRI and clinical assessments repeated at the second visit; 10 HC (4 female (F), mean age (SD): 43.4 (8.9) years), 10 RRMS (6 F, 40.5 (9) years), 10 SPMS (4 F, 56.3 (5.9) years) and 10 PPMS (2 F, 56.2 (8.5) years). The mean (SD) follow-up visit for the HC was (14 (5.2) months), RRMS (24 (3.74) months), SPMS (16.3 (3.6) months) and PPMS (14.8 (4.9) months).

Informed written consent was obtained from each study participant prior to inclusion in the study. The study received approval from the local Institutional Ethics Committee.

2.2. MRI acquisition protocol

Imaging was performed using a 3 T Philips Achieva MRI system with RF dual-transmit technology (Philips Medical Systems, Best, Netherlands) and the manufacturer's product 16-channel neurovascular coil.

The whole cervical cord was imaged using a magnetization-prepared 3D T1-weighted acquisition (with isotropic voxel size of 1 mm^3) in the sagittal plane with FOV = 256 × 256 mm^2, matrix size = 256 × 256, TR = 8 ms, TE = 3.7 ms, TI = 860 ms (using linear *k*-space profile order), SENSE = 2 in the anterior–posterior direction and TFE factor of 205; the scan time for the acquisition was 6:30 min.

2.3. Image analysis

The 3D T1-weighted volume obtained from each study participant was processed using both the active surface (*AS*) (Horsfield et al., 2010) (Jim 6.0_019; http://www.xinapse.com/) and *PropSeg* (De Leener et al., 2014) (Spinal Cord Toolbox version 1.0; https://sourceforge.net/projects/spinalcordtoolbox/) segmentation methods in two different ways, which provide the CSA at C2/C3 and between C2 and C5, respectively: i) by reformatting the original sagittal volume in the axial plane and extracting 15 contiguous 1 mm thick slices orthogonal to the longitudinal axis of the cervical cord centred at the C2/C3 level – this was done using the multi-planar reconstruction option available within Jim 6.0 that allows to manually position the handle of the reformatted volume orthogonal to the longitudinal axis of the cervical cord centred at the C2/C3; the volume was subsequently resampled using sinc interpolation along the slice direction – and ii) by using the axial reformatted volume obtained from i), only this time processing a larger number of axial slices to cover the section of the cervical cord from the top of C2 to the base of C5 vertebral body as

Table 1
Demographic and clinical characteristics of study participants at baseline.

	Controls n = 26	CIS n = 21	RRMS n = 26	SPMS n = 21	PPMS n = 26
Gender (F:M)	17:9	13:8	17:9	12:9	11:15
Mean age (±SD)	42 (10.5)	35 (9)	40 (10)	51 (10)	51 (9)
Mean disease duration (years/months for CIS)	N/A	5	7	19	10
Mean CSA (±SD) — *PropSeg* (C2/C3)	70.2 (7.4)	75.9 (7.9)	68.6 (7.7)	56.2 (10.1)	61.1 (9.3)
Mean CSA (±SD) — *AS* (C2/C3)	75.8 (7.7)	82.0 (8.2)	74.0 (7.3)	62.0 (10.5)	67.1 (10.6)
Mean CSA (±SD) — *PropSeg* (C2/C5)	72.4 (7.1)	77.9 (7.9)	71.3 (7.9)	58.2 (10.0)	62.5 (9.0)
Mean CSA (±SD) — *AS* (C2/C5)	78.7 (7.4)	84.7 (8.0)	77.5 (8.0)	64.4 (10.4)	69.8 (9.7)
Median EDSS (range)	N/A	1 (0–3.5)	3 (0–6.5)	7 (4.5–7.5)	6 (2–7)
Median TWT (range)	5 (4–6)	4.6 (3.4–9.8)	5.7 (3.4–9.6)	22.3 (5–180)	8.3 (5–180)
Median HPT (range)	18.9 (15.1–27.1)	20.7 (16.6–25.4)	20.5 (15–36.4)	29.6 (19.1–200.8)	28.9 (17.1–179.6)
Mean PASAT (±SD)	53 (5.3)	45.2 (9.4)	41.6 (14.6)	37 (19.2)	34.9 (18.8)
Median ASIA-m (range)	100 (–)	100 (98–100)	99 (74–100)	87 (63–98)	85 (54–100)
Median ASIA-s (range)	112 (–)	112 (84–112)	110 (98–112)	104 (84–112)	101.5 (90–112)

CIS: clinically isolated syndrome; RRMS: relapsing remitting MS; PPMS: primary progressive MS; SPMS: secondary progressive MS; EDSS: expanded disability status score; TWT: 25-foot timed walk test; HPT: 9-hole peg test; PASAT: 3 s paced auditory serial addition test B; ASIA: American Spinal Injury Association motor (m) and sensory (s) scores; SD: standard deviation.